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Clinical efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum β-lactamase-producing *Enterobacteriaceae* in haematological patients with neutropaenia: a study protocol for a retrospective observational study (BICAR)

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ABSTRACT

Introduction: Bloodstream infection (BSI) due to extended-spectrum β-lactamase-producing Gram-negative bacilli (ESBL-GNB) is increasing at an alarming pace worldwide. Although β-lactam/β-lactamase inhibitor (BLBLI) combinations have been suggested as an alternative to carbapenems for the treatment of BSI due to these resistant organisms in the general population, their usefulness for the treatment of BSI due to ESBL-GNB in haematological patients with neutropaenia is yet to be elucidated. The aim of the BICAR study is to compare the efficacy of BLBLI combinations with that of carbapenems for the treatment of BSI due to an ESBL-GNB in this population.

Methods and analysis: A multinational, multicentre, observational retrospective study. Episodes of BSI due to ESBL-GNB occurring in haematological patients and haematopoietic stem cell transplant recipients with neutropaenia from 1 January 2006 to 31 March 2015 will be analysed. The primary end point will be case-fatality rate within 30 days of onset of BSI. The secondary end points will be 7-day and 14-day case-fatality rates, microbiological failure, colonisation/infection by resistant bacteria, superinfection, intensive care unit admission and development of adverse events.

Sample size: The number of expected episodes of BSI due to ESBL-GNB in the participant centres will be 260 with a ratio of control to experimental participants of 2.

Strengths and limitations of this study

- The multicentric design of the study will allow the recording of a large number of episodes.
- The impact of therapy on mortality and other relevant outcomes will be assessed.
- Owing to the retrospective design of the study, some information may be lost.
- We may not be able to control for some measured and unmeasured confounders.
- Enrolling a sufficient number of patients treated with β-lactam/β-lactamase inhibitor combinations may be difficult.

Ethics and dissemination: The protocol of the study was approved at the first site by the Research Ethics Committee (REC) of Hospital Universitari de Bellvitge. Approval will be also sought from all relevant RECs. Any formal presentation or publication of data from this study will be considered as a joint publication by the participating investigators and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE). The study has been endorsed by the European Study Group for Bloodstream Infection and Sepsis (ESGBIS) and the European Study Group for Infections in Compromised Hosts (ESGICH).

INTRODUCTION

The recent spread of extended-spectrum β-lactamases (ESBLs) in *Enterobacteriaceae* has become a serious public health problem worldwide.[1 2] Bloodstream infection (BSI) due to these multidrug-resistant (MDR) microorganisms is increasingly recognised among patients with haematological malignancies and in haematological stem cell transplant (HSCT) recipients, who in addition, present an increased risk of severe sepsis and death.[3–6]

Until recently, carbapenems, which are not affected by ESBLs, were considered the drugs of choice for treating severe infections caused by ESBL producers.[1 2] For this reason, while clinicians await new antimicrobials with activity against these MDR microorganisms, they have often been forced to use carbapenems as empiric or definitive therapy in patients with suspected or documented infections due to an ESBL-producing organism. However, the increasing use of carbapenems is particularly worrisome in a scenario in which carbapenemase-producing organisms are also emerging as a serious health problem.[7 8] Thus, the search for alternatives to carbapenems for infections caused by ESBL producers is a priority. Although ESBL-producing bacteria may also have different resistance mechanisms that restrict the activity of β-lactam/β-lactamase inhibitor (BLBLI) combinations, some of these agents remain active against a considerable proportion of ESBL-producing enterobacteria, particularly *Escherichia coli*.[9 10]

Recent investigations, including two systematic reviews, suggest that the combination of a BLBLI may be a reliable option for the treatment of BSI due to ESBL-producing Gram-negative bacilli (ESBL-GNB), especially in non-immunocompromised patients.[11–16] Conversely, other studies have found higher mortality rates in patients with BSI due to ESBL-GNB who received piperacillin-tazobactam (PTZ) compared with those treated with carbapenems.[17–19] The impact of the minimum inhibitory concentration (MIC) of PTZ on outcomes of patients with these severe infections who receive this regimen has also been questioned.[19 20]

Until now, the efficacy and safety of BLBLI combinations for the treatment of BSI due to ESBL-GNB in HSCT recipients and haematological patients with neutropaenia has not been elucidated. These patients are particularly prone to develop life-threatening infections and frequently receive broad-spectrum antibiotics.

This study aims to evaluate if BLBLI combinations are as effective as carbapenems for the treatment of ESBL-GNB BSI in this high-risk population.

OBJECTIVES OF THE STUDY

Primary end point

To compare the efficacy of BLBLI combinations with that of carbapenems for the treatment of BSI due to ESBL-GNB in haematological patients with neutropaenia, in terms of a 30-day case-fatality rate.

Secondary end points

To compare the rates of the following events in these two groups of patients:

1. Seven-day and 14-day case-fatality rates.
2. Microbiological failure, defined as the presence of at least one of the following criteria:
   A. Persistent BSI beyond the first 48 hours of adequate antibiotic therapy.
   B. Relapse of BSI within 7 days of treatment discontinuation.
3. Colonisation/infection by bacteria resistant to the study antibiotics.
4. Any bacterial superinfection other than ESBL-GNB.
5. Intensive care unit admission.
6. Development of adverse events:
   A. Any adverse event.
   B. Adverse events requiring treatment discontinuation.

METHODS AND ANALYSIS

Study design

A multinational, multicentre, retrospective, observational cohort study involving the collection of data of patients from 1 January 2006 to 31 March 2015.

The study will be conducted in accordance with the STROBE recommendations.[21]

Study population

Data will be collected on haematological patients with neutropaenia with at least one episode of BSI due to an ESBL-producing *Enterobacteriaceae* and who receive carbapenems or BLBLI combinations as the empirical or definitive antibiotic therapy.

Setting

The study will be conducted at 22 centres from nine different countries: Spain (11 centres), Brazil (3 centres), Argentina (2 centres), Australia (1 centre), Canada (1 centre), Germany (1 centre), Italy (1 centre), Turkey (1 centre) and the USA (1 centre). The great majority of participating centres (20) are university hospitals, except for Hospital Rawson in San Juan, Argentina and Barcelona Hospital in Barcelona, Spain.

Selection of cases

Patients will be identified from previous prospective databases or from the records of the microbiology laboratory of each hospital.

Inclusion criteria

1. Adult patients (≥18 years).
2. Patients with haematological diseases and/or HSCT recipients, both autologous and allogeneic.
3. The presence of neutropaenia (<500 neutrophils/mm^3) at onset of the episode of BSI.
4. Episodes of monomicrobial BSI due to any species of ESBL-producing *Enterobacteriaceae*, including

community, healthcare and nosocomial infections. ESBL production would have been screened in all isolates with diminished susceptibility to cephalosporins and confirmed according to standard procedures. The ESBLs would have been identified by using phenotypic or molecular methods, when needed.

5. Antibiotic therapy with a BLBLI combination or a carbapenem for at least 24 hours. A 24-hour course of antibiotics might not be enough to optimally evaluate its impact on outcomes. However, since carbapenems have been the recommended treatment for serious ESBL infections, it could be very difficult to collect patients who have received a long course of BLBLI therapy. Moreover, the empirical antibiotic therapy administered to a high-risk neutropaenic patient with Gram-negative BSI within the first 24 hours has probably the highest impact on outcome.
6. Subsequent episodes in a patient caused by the same organism may be included if the interval between them is >1 month.

Exclusion criteria

Patients with any of the following will be excluded from the study:

1. Episodes of polymicrobial BSI.
2. Unavailability of key data (data regarding empirical and targeted therapy and mortality).
3. Episode occurring outside the study period.
4. Age <18 years.

Data collection

Patients' data will be collected retrospectively. These data will be obtained from various sources, including patients' electronic records, patients' notes, the hospital laboratory systems and the hospital patient administration system.

The following data will be collected for all cases: sex, age, underlying disease and comorbidities, haematological malignancy status, severity of the episode of febrile neutropaenia according to the Multinational Association of Supportive Care in Cancer (MASCC) index score,[22] place of acquisition of infection,[23] source of BSI, BSI source control status, clinical and microbiological data, duration of neutropaenia, prior therapies received (antibiotics, immunosuppressors, etc), empirical and definitive antimicrobial therapy, reason for change of antimicrobial therapy, duration of each antibiotic therapy, need for intensive care unit admission and mechanical ventilation, persistent BSI, relapse of BSI, colonisation and/or superinfection by resistant organisms, development of other complications, 7-day case-fatality rate, 14-day case-fatality rate, 30-day case-fatality rate, and development of adverse events.

Definitions

- Antimicrobial therapy administered before susceptibility results were available will be considered as empirical therapy, and antibiotic therapy administered afterwards will be considered as definitive.
- Therapy with a BLBLI combination or a carbapenem will be considered as monotherapy if no other drug with activity against Gram-negatives was co-administered, irrespective of the isolate susceptibility.
- Adverse events will include any of the following events: moderate or severe allergic reactions, severe renal impairment, severe liver impairment and seizures.

Participant timeline

The follow-up period will last 1 month after the onset of BSI.

Study outcomes and end point assessment

Primary end point

- Case-fatality rate at 30 days from onset of BSI.

Secondary end points

- Seven-day and 14-day case-fatality rates from onset of BSI.
- Time to death, in days.
- Microbiological failure, defined by:
  - Persistent BSI beyond the first 48 hours of adequate antibiotic therapy.
  - Relapse of BSI within 7 days of treatment discontinuation.
- Rate of colonisation/infection by bacteria resistant to the study antibiotics.
- Rate of superinfection due to any bacteria.
- Rate of intensive care unit admission.
- Rates of adverse events including:
  - Any adverse event.
  - Adverse events requiring treatment discontinuation.

Sample size

The total number of episodes of BSI due to ESBL-GNB in the participant centres during the study period will determine the sample size. We expect an amount of 260 episodes with a ratio of control to experimental participants of 2. Prior data indicate that the 30-day case-fatality rate among controls is 17%. Thus, with an α risk of 0.05 and a β risk of 0.2 in a two-sided test, we will be able to detect a true 30-day case-fatality rate of 5% or 32% in exposed participants. We will use an uncorrected χ^2 statistic to evaluate this null hypothesis.

Statistical analysis

Patients who were given BLBLI will be compared with those who were treated with carbapenems empirically and/or as definitive therapy.

Two non-mutually exclusive cohorts will be constructed and analysed separately. The empirical therapy cohort (ETC) will include patients who received empirical therapy with BLBLI or carbapenem, and the isolate was susceptible to the empirical antimicrobial administered. The definitive therapy cohort (DTC) will include

patients who received definitive monotherapy with an active BLBLI or carbapenem.

Continuous variables will be compared by means of the Mann-Whitney U test and t-test. Qualitative variables will be compared using the χ^2 test, and relative risks and 95% CIs will be calculated.

We will use an uncorrected χ^2 statistic to evaluate the primary end point under the null hypothesis of a 30-day case-fatality rate between study groups. Mortality survival functions of patients treated with BLBLI or carbapenems will be estimated using Kaplan-Meier curves and compared using a log-rank test. Moreover, survival functions will be compared also at days 7, 14 and 30 to detect very early, early or late mortality differences. To control for confounding, multivariate analysis will be performed by the Cox proportional hazard model, using time until death as the dependent variable and therapy with BLBLI or carbapenem as the explanatory variable of interest. In both cohorts (ETC and DTC), a propensity score for receiving carbapenem as empirical therapy will be added to the model. The propensity score—the probability of receiving carbapenem as empirical and/or targeted therapy—will be calculated using a non-parsimonious multivariate logistic regression model in which the outcome variable will be the use of carbapenem as empirical therapy. Each patient will be matched to another patient using the nearest participant matching technique. The analysis will be performed with the stepwise logistic regression model of R software (R V.3.2.5).

ETHICAL ISSUES

Prior to the initiation of the study at a particular site, approval will be sought from all appropriate regulatory agencies and the local Research Ethics Committees (RECs) to conduct the study in accordance with the local regulatory requirements. The study will only use data routinely collected in the time frame January 2006 to March 2015. No extra tests or interventions will be undertaken in patients and the study will have no impact on patient care or outcome.

The processing of the patients' personal data collected in this study will comply with the European Directive on Data Privacy. All data will be collected, stored and processed anonymously (EU Directive 95/46/EC).[24] All data will be stored in a specific database.

The protocol (V2.0 15/5/2015) was approved on 21/5/2015 by the REC at the first site. The need for informed consent and information sheets was waived by the REC because of the retrospective nature of the study.

Publication plan

Results will be reported at conferences and in peer-reviewed publications. The first publication is based on data from all sites, and is analysed as stipulated in the protocol with supervision by statisticians. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigators and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE).

DISCUSSION

The emergence and dissemination of ESBL-GNB has become a serious problem worldwide, and is especially worrisome in immunosuppressed patients with cancer and HSCT recipients, who are at risk of severe infection and death.[3–6]

Until recently, carbapenems have been regarded as the drugs of choice for the treatment of serious ESBL-GNB infections such as BSI. They have been widely used for the treatment of patients with suspected or documented infections due to these organisms. However, their overuse may induce the appearance of resistance to this agent,[25 26] thus severely limiting future treatment options. This possibility is of particular concern in a scenario in which carbapenemase-producing organisms are also spreading and are adversely compromising patient's outcomes.[26 27] Therefore, it is extremely important to identify therapeutic alternatives to these drugs.

The published data on the use of BLBLI combinations for the treatment of infections caused by ESBL-GNB are conflicting.[11–19] In addition, different factors may be involved in the outcomes of patients treated with these drugs, such as type of infection, the 'inoculum effect' to PTZ (ie, diminished activity with the presence of high bacteria inoculum), the impact of the MIC of this drug and the potential increase in efficacy when using high doses.[19 20 28] Moreover, the existing literature includes mainly non-immunocompromised patients, and information is lacking regarding the usefulness of these agents for the treatment of BSI due to ESBL-GNB in high-risk haematological patients with neutropaenia, including HSCT recipients.

The studies performed in the general population addressing this issue usually carry methodological challenges, which may also be observed in the present study.[13–19] First, all reported studies are retrospective.[13–19] Randomised controlled trials comparing empirical and definitive antibiotic regimens are difficult to perform in this setting. Nevertheless, a randomised clinical trial is being undertaken in several Australasian sites, including Singapore (the 'MERINO' trial, registered at http://www.clinicaltrials.gov; NCT02176122), and aims to be completed by 2018. Second, most of the published studies involve patients with BSI from the urinary tract, and the results may not be generalisable to patients with other sources of BSI.[13–16 19] Third, the BLBLI usually studied is PTZ and, less frequently, amoxicillin-clavulanate; therefore, the results should not be extended to other newer BLBLI currently being developed, until more data are available.[13–19] Finally, information regarding the MIC for PTZ,[15–17] as well as the doses used for each antibiotic, may not be available in all studies.[14 16 18]

This study aims to assess the efficacy of BLBLI combinations in comparison with carbapenems for the treatment of high-risk immunocompromised haematological patients with BSI due to ESBL-producing *Enterobacteriaceae*. It is expected to provide important information regarding the usefulness of BLIBLI combinations as carbapenem-sparing antibiotic regimens for infections caused by ESBL-GNB, which represents a key step in the efforts to minimise the spread of carbapenem-resistant microorganisms. Information on this issue will be particularly important in a population prone to receive frequent, repeated cycles of broad-spectrum antibiotics, and which often presents with serious or life-threatening infections.

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Contributors All authors were involved in the study concept. CG, CR-C, CT and JC were involved in the design of the study. CG, CR-C, AC, MG, BM, GM-dIC, IR-C, NL, MV, LLS, MDN, MC, RA, JALJ, LG, YM, RE, JLJ, PM-D, MP, AC, ES, GM, TG, RN, HD, PHO, LCP, KYI, AF, CC, DK, FH and AM were responsible for identification of the cases and data collection. CT was the statistician in charge of the statistical analysis. CG and JC drafted and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Competing interests JR-B has been a scientific consultant for Merck, AstraZeneca, Achaogen and InfectoPharm, a speaker in accredited educational activities for Merck and AstraZeneca, a recipient of research grants from COMBACTE-NET, COMBACTE-CARE and COMBACTE-MAGNET, funded by the Innovative Medicines Initiative (European Union and EFPIA in kind). AF has received research fees from Merck, and from Astellas for data and safety monitoring. JC has received lecture fees from Novartis, Astellas, Pfizer, MSD, Janssen and Astra-Zeneca.

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